June 14, 2024

Akili Interactive Labs, Inc.
% Bhupinder Singh
Head of Quality and Regulatory Affairs
22 Boston Wharf Rd 7th Floor
Boston, MA 02110

Re: K233496
Trade/Device Name: EndeavorOTC
Regulation Number: 21 CFR 882.5803
Regulation Name: Digital therapy device for attention deficit hyperactivity disorder
Regulatory Class: Class II
Product Code: QFT
Dated: May 16, 2024
Received: May 16, 2024

Dear Bhupinder Singh:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device"

(https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Robert Kang -S

for Pamela Scott, MS
Assistant Director
DHT5B: Division of Neuromodulation
and Physical Medicine Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K233496

Device Name
EndeavorOTC

Indications for Use *(Describe)*
EndeavorOTC is a digital therapeutic indicated to improve attention function as measured by computer-based testing in patients 18 and older with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorOTC demonstrate improvements in a digitally assessed measure, Test of Variables of Attention (TOVA®) of sustained and selective attention and may not display benefits in typical behavioral symptoms such as hyperactivity. EndeavorOTC is not intended to be a replacement for any form of treatment and should be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

Type of Use *(Select one or both, as applicable)*

☐ Prescription Use (Part 21 CFR 801 Subpart D) ☒ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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7. 510(k) Summary

This 510(k) summary of safety and effectiveness information is prepared in accordance with 21 CFR § 807.92.

Date Prepared:	October 30, 2023
Legal Manufacturer:	Akili Interactive Labs, Inc. 71 Commercial St Mailbox 312 Boston, MA 02109
Primary Contact Person:	Bhupinder Singh Head of Quality and Regulatory Affairs Phone: +1 (408) 832-7124 E-mail: bsingh@akiliinteractive.com

Regulatory Information

Device Trade Name:	EndeavorOTC
Device Classification Name:	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder
Regulation Number:	21 CFR § 882.5803
Classification Product Code:	QFT
Review Advisory Committee:	Neurology
Device Classification:	Class II
510(k) Number	K233496

Predicate Device Information

Device Manufacturer:	Akili Interactive Labs, Inc.
Submission Number:	DEN200026
Device Name:	EndeavorRx
Other Reference Device	EndeavorRx (K231337)

Device Description:

EndeavorOTC is software-as-a-medical device (SaMD) that resides on the user's mobile device and can be executed at home.

It is an over-the-counter (OTC) digital therapeutic indicated to improve attention function as measured by computer-based testing in patients 18 and older with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorOTC demonstrate improvements in a digitally assessed measure, Test of Variables of Attention (TOVA®) of sustained and selective attention and may not display benefits in typical behavioral symptoms such as hyperactivity. EndeavorOTC is not intended to be a replacement for any form of treatment and should be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

The device is built on Akili's proprietary, patented, technology platform. EndeavorOTC uses adaptive algorithms (also known as Selective Stimulus Management Engine, SSME™) to deliver stimuli that are designed to engage the patient in a manner that improves their attention function. In a closed-loop system, the adaptive SSME™ algorithms automatically adjust the difficulty level for a personalized treatment experience that is tailored to the needs of each individual patient.

EndeavorOTC is delivered through a video game experience which leverages art, music, storytelling, and reward cycles to keep patients engaged. The adaptive algorithm constantly pushes patients precisely at predefined performance bounds relative to each individual, such that they are continuously encouraged to exceed their historic performance. The science behind EndeavorOTC was developed at the University of California, San Francisco by Adam Gazzaley, M.D., Ph.D., Founding Director of the University of California San Francisco's Neuroscape and Akili's Chief Science Advisor.

The basic program inputs are steering, which is accomplished by using the mobile device's internal accelerometer to measure the degree to which it is tilted, and tapping, which is accomplished using the touch screen to measure correct and incorrect targeting. The basic outputs are the visual display of the game progression along with audio, which is accomplished by using the internal high resolution display and internal speaker. The program includes features to ensure it is used per the recommended regimen (approximately 25 minutes per day, 5 days per week, for 6 weeks).

Indications for Use:	EndeavorOTC is a digital therapeutic indicated to improve attention function as measured by computer-based testing in patients 18 and older with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorOTC demonstrate improvements in a digitally assessed measure, Test of Variables of Attention (TOVA®) of sustained and selective attention and may not display benefits in typical behavioral symptoms such as hyperactivity. EndeavorOTC is not intended to be a replacement for any form of treatment and should be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.
Limitations	EndeavorOTC may not be appropriate for users with photo-sensitive epilepsy, color blindness, or physical limitations that restrict use of a mobile device. It is recommended that users speak to their health care provider before starting EndeavorOTC treatment. EndeavorOTC is not for persons who have a comorbid psychiatric condition in addition to ADHD. When using this device it is recommended that users seek care from a medical health care provider in conjunction with its use. NOTE: This single arm study did not include a sham control group and it is therefore possible that observed effects were due to bias or placebo effects. Akili has conducted and published additional studies that support the lack of a placebo effect on the TOVA[1,2]. Patients and health care providers should consider the totality of the clinical evidence in light of this before using this product.

[1] Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7

[2] Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125

Summary of Technological Characteristics

Attribute	Subject Device: EndeavorOTC	Predicate Device: EndeavorRx (DEN200026)	Comparison
Manufacturer	Akili Interactive Labs, Inc.	Akili Interactive Labs, Inc.	Same
Device Classification Name	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder	Digital Therapeutic Software for Attention Deficit Hyperactivity Disorder	Same
Product Code	QFT	QFT	Same
Regulation Number	21 CFR § 882.5803	21 CFR § 882.5803	Same
Intended use	Digital therapeutic adaptive stimulus software for the closed-loop treatment of psychiatric disorders and cognitive dysfunction associated with medical conditions.	Digital therapeutic adaptive stimulus software for the closed-loop treatment of psychiatric disorders and cognitive dysfunction associated with medical conditions.	Same
Indication of Use	EndeavorOTC is an over the counter digital therapeutic indicated to improve attention function as measured by computer-based testing in patients 18 and older with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorOTC demonstrate improvements in a digitally assessed measure, Test of Variables of Attention (TOVA®) of sustained and selective attention and may not display benefits in typical behavioral symptoms such as hyperactivity.	EndeavorRx is a digital therapeutic indicated to improve attention function as measured by computer based testing in children ages 8-12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx demonstrate improvements in a digitally assessed measure Tests of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. EndeavorRx should be considered for use as part of a therapeutic program	Substantially equivalent. EndeavorOTC is indicated for 18 years of age or older, compared to the predicate device (8-12 years). The difference in age range do not change the intended use of the device, and clinical testing demonstrates the subject device is safe and effective in the adult population.

	EndeavorOTC is not intended to be a replacement for any form of treatment and should be used as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder	that may include: clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.	Product indication was changed from Rx to OTC. See Access row below for further discussion.
System Components	Patient facing video game application Mobile device platform	Patient facing video game application Mobile device platform	Same
Proprietary Algorithm	Selective Stimulus Management Engine (SSMETM)	Selective Stimulus Management Engine (SSMETM)	Same
Basic Operations	Steering, Tapping, Multi-tasking	Steering, Tapping, Multi-tasking	Same
Presentation	Structured manner across game "Challenges" and "Worlds"	Structured manner across game "Challenges" and "Worlds"	Same
Mobile Platform Compatibility	iOS and Android	iOS and Android	Same
Access	Over-the-counter use. It is recommended that patients speak to their health care provider before starting EndeavorOTC treatment. See section, "Summary of Clinical Performance Data" below for supporting data.	Prescription use only. Authorized and overseen by a licensed health care provider.	Labeling modifications were made to support over-the-counter use, and human factors validation testing confirms the change to OTC does not raise different questions.

Summary of Non-Clinical Performance Data:

Bench software testing has been performed on the EndeavorOTC and demonstrates compliance with the following international and FDA-recognized consensus standards and FDA guidance documents:

- **ISO 14971:2019** Medical devices - Application of risk management to medical devices
- **IEC 62304 Edition 1.1 2015-06 CONSOLIDATED VERSION** Medical device software - Software life cycle processes
- **IEC 82304-1 Edition 1.0 2016-10** Health software - Part 1: General requirements for product safety
- FDA Guidance Document for Industry and FDA Staff - *Content of Premarket Submissions for Device Software Functions - Guidance for Industry and Food and Drug Administration Staff* (Final Guidance issued June 14, 2023)
- FDA Guidance Document for Industry and FDA Staff - *Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions: Guidance for Industry and Food and Drug Administration Staff* (Final Guidance issued September 27, 2023)

The results of bench software verification and validation testing supports that EndeavorOTC functions as intended.

Human factors validation testing was performed to ensure that EndeavorOTC is safe and effective for intended users, use, and use environments, and demonstrates compliance with the following additional standards and guidance document:

- **ANSI/AAMI/IEC 62366-1:2015/ Amd 1: 2020** Medical Devices - Part 1: Application of Usability Engineering to Medical Devices - Amendment 1
- **ANSI/AAMI/IEC 62366-2:2016** Medical Devices - Part 2: Guidance on the application of usability engineering to medical devices
- FDA Guidance Document for Industry for Industry and FDA Staff - *Applying Human Factors and Usability Engineering to Medical Devices*, issued February 3, 2016

The results of the human factors validation testing supports the usability of EndeavorOTC in intended users, for the intended use, in the intended use environment.

Summary of Clinical Data:

Clinical performance testing was conducted to evaluate the efficacy and safety of EndeavorOTC in adults 18 years of age and older.[3] Efficacy was determined primarily by the change from baseline in a digitally assessed measure of sustained and selective attention, the Test of Variables of Attention (TOVA®), after 6 weeks of treatment. The multi-center open-label study enrolled 221 subjects with inattentive or combined-type ADHD. A diagnosis of ADHD was determined in study participants using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as confirmed by the Mini-International Neuropsychiatric Interview (MINI) for ADHD adult version 7.0.2. All 221 participants who were enrolled in the adult study were included in the Safety population (also known as ITT or intent to treat population, is all subjects enrolled in the study), and 153 participants were included in the Efficacy Population (also known as the mITT or modified intent to treat population, is all enrolled subjects with drop outs excluded). Safety population is all participants who were exposed to AKL-T01 intervention. Efficacy population is all participants who took the AKL-T01 intervention home and completed both baseline and day 42 exit visit assessments (including TOVA).

Seventy-five participants (33.9%) discontinued the study: the most common reason for study discontinuation was withdrawal by participant. Reasons for withdrawal by participants include the following: experiencing technical bugs or technical issues; game took too much time away from school, work, or other activities; did not like AKL-T01; did not want to complete the on-site study activities any further. Three (1.7%) participants discontinued the study due to adverse events (1 headache, 2 nausea).

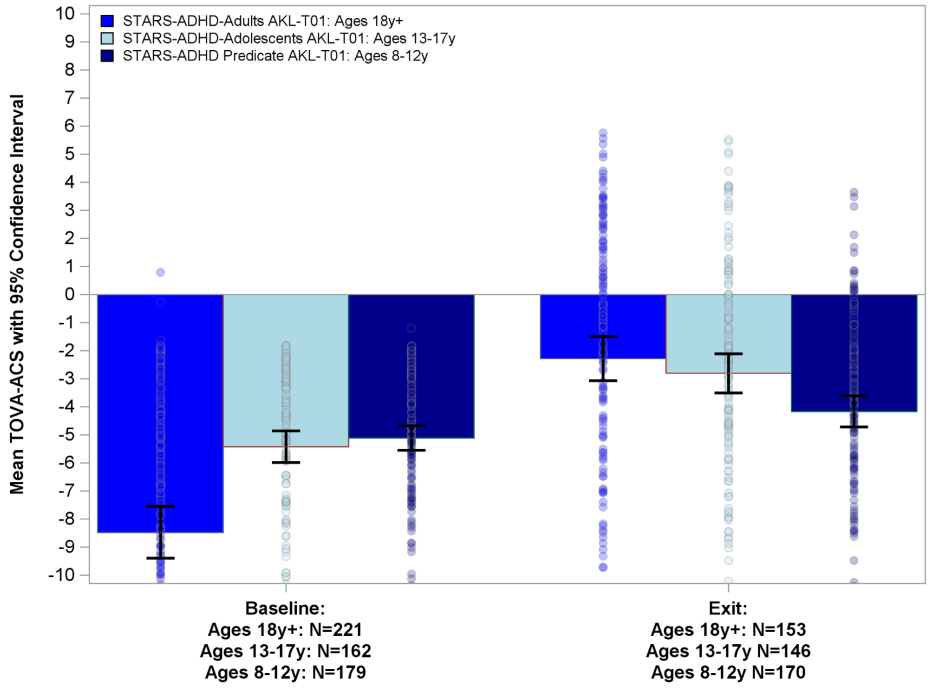
For further description of the adult study in comparison to the predicate studies, see **Table 1** - comparison of clinical study design description.

The results of the clinical performance study support the performance and safety of EndeavorOTC in the adult age range. Analysis of the primary efficacy endpoint in the Efficacy Population (N=153) showed a statistically significant positive mean change from baseline to study day 42 in the TOVA of 6.460 (SD 6.9522 [95% CI: 5.349, 7.570]; $P < 0.0001$). **Figure 1** below compares the mean TOVA-ACS score from participants in the STARS-Adult study (subject study) with STARS-Adolescents (K231337) and STARS-ADHD (DEN200026) studies. Analysis of the

[3] Stamatis, C. A., Mercaldi, C., & Kollins, S. H. (2023). A Single-Arm Pivotal Trial to Assess the Efficacy of Akl-T01, a Novel Digital Intervention for Attention, in Adults Diagnosed With ADHD. Journal of the American Academy of Child & Adolescent Psychiatry, 62(10), S318

secondary efficacy endpoints in the Efficacy Population (N=153) showed improvements in the ADHD-RS total score by a mean of 8.3 points (SD: 7.74) and in the ADHD-RS inattentive score by a mean of 5.1 points (SD: 4.78). The improvements observed did not meet clinically meaningful improvement, which is estimated as 10-point difference in Total Score based on literature.[4] For a comparison of clinical study outcomes between the subject and predicate studies, see **Table 2.**

Figure 1. Mean TOVA-ACS Score Bar Chart Comparison across Subject and Predicate Studies



Markers represent individual subject values. Two participants in STARS-ADHD-Adults were enrolled that did not meet inclusions criteria of baseline TOVA-ACS ≤ -1.8 and were reported as protocol violations. TOVA-ACS scores below zero suggest performance similar to individuals with ADHD.[5]

Study results were based on a modified intent-to-treat (mITT, also known as Efficacy population, is all enrolled subjects with drop outs excluded) population. This population included all enrolled participants with sufficient data at baseline and exit to calculate change scores (N=153) instead of the intent-to-treat (ITT, also known as Safety Population, is all subjects enrolled in the study) population (N=221).

[4] Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. Int J Methods Psychiatr Res. 2005;14(4):186-201. doi:10.1002/mpr.7

[5] *TOVA Clinical Manual 2020, p. 32 of 78:* https://files.tovatest.com/documentation/9/Clinical%20Manual.pdf

A sensitivity analysis using multiple imputation (MI) was performed to assess the impact of missing exit data in the ITT population. Change in TOVA-ACS was generally similar in the ITT population after imputation, with a mean [95% CI] of 6.144 [5.037, 7.273] as compared with the mITT population 6.460 [5.349, 7.570]. See **Table 3** for a Modified Intent-to-Treat (mITT) and Intent-to-Treat (ITT) Analysis with Multiple Imputation (MI) of the Primary Efficacy Endpoint - TOVA-ACS Change from Baseline to Exit.

Overall, 11 (5.0%) subjects experienced a treatment-emergent adverse device event (TE-ADE). Reports include 4 (1.8%) nausea, 3 (1.4%) headaches, 2 (0.9%) decreased frustration tolerance, and 1 each (0.5%) of arthritis, dizziness, fatigue, and somnolence. All TE-ADEs were mild or moderate. There were no serious adverse device events. See **Table 4** for a comparison of clinical safety outcomes from the subject study with predicate studies.

Akili has conducted and published additional studies that support the lack of a placebo effect on the TOVA[6,7]. Patients and health care providers should consider the totality of the clinical evidence in light of this before using this product.

The clinical performance study demonstrates that EndeavorOTC is safe and effective for its intended use in the indicated patient population.

NOTE: This single arm study did not include a sham control group and it is therefore possible that observed effects were due to bias or placebo effects. Users should consider the totality of the clinical evidence in light of this before using the product.

Some persons with known comorbid psychiatric conditions were excluded from this study and therefore the risk profile for persons with comorbid psychiatric conditions is not fully known.

[6] Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7

[7] Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125

Table 1. Clinical study design description comparison

	Subject Device K233496	Predicate Device DEN200026	
	STARS-Adult Study (ages 18+)	**STARS Study (ages 8-12)**	**Comparison describing differences and a rationale why it is acceptable**
Population	Verified ADHD diagnosis with impaired attention; on or off medication	Verified ADHD diagnosis with impaired attention; medication exclusionary	SIMILAR - the adult study allowed for medication as long as use was stable for ≥4 weeks prior to study enrollment and throughout the study. A prior study demonstrated benefits of intervention on the pediatric population with ADHD both on and off medication.
Study Design	Single arm, open-label, adaptive design	Randomized clinical trial	DIFFERENT - Presence of attentional improvement from treatment compared to those on active control was established in the STARS study. The adult study investigated the magnitude of improvement and safety in the new age range. The Adult study used an adaptive design based on the total information as measured by the standard error of the primary endpoint which would allow the trial to be stopped prior to recruitment of the 325 participants derived from the sample size calculations. The adaptive design accounts for the uncertainty regarding whether the variation in TOVA-ACS mean change differed between the adult and pediatric ADHD populations. The safety and effectiveness of the exact same device was established in an RCT De Novo in a younger population. The primary endpoint used in the current study was identical to the original STARS RCT. Based on the predicate RCT, the primary outcome measure TOVA demonstrates less susceptibility to placebo effect in the

			randomized, controlled trial utilized for the de novo. Another consideration for the single arm design is that the TOVA-ACS is less susceptible to placebo effects when measuring attentional control processes within the context of ADHD, as supported by the predicate RCT and multiple published studies in the literature.[8,9,10]
Intervention	EndeavorRx (AKL-T01)	EndeavorRx (AKL-T01) EVO: Words (Active control)	SIMILAR - All use the same active intervention, minor differences in software.
Treatment regimen	25 minutes/day for 5 days/week	25 minutes per day, 5 days per week	SIMILAR
Participant Duration	Approximately 6 weeks on treatment	Approximately 4 weeks on treatment	DIFFERENT - In Adults, treatment duration was adjusted to match duration used in past adult studies using a similar SSME™-driven product
Diagnosis of ADHD	Yes - Diagnosis of ADHD combined or inattentive type, required according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as confirmed by Mini International Neuropsychiatric Interview (MINI) for Attention – Deficit / Hyperactivity	Yes - Confirmed ADHD diagnosis, any presentation, required at Screening based on DSM-V criteria and established via the MINI-KID administered by a trained clinician	SIMILAR - An age-appropriate version of the MINI was used in the adult study.

[8] Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital Intervention for Cognitive Deficits in Major Depression: A Randomized Controlled Trial to Assess Efficacy and Safety in Adults. Am J Psychiatry. 2022;179(7):482-489. doi:10.1176/appi.ajp.21020125

[9] Yerys BE, Bertollo JR, Kenworthy L, et al. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J Autism Dev Disord. 2019;49(4):1727-1737. doi:10.1007/s10803-018-3856-7

[10] Murray DW, Childress A, Giblin J, Williamson D, Armstrong R, Starr HL. Effects of OROS methylphenidate on academic, behavioral, and cognitive tasks in children 9 to 12 years of age with attention-deficit/hyperactivity disorder. Clin Pediatr (Phila). 2011;50(4):308-320. doi:10.1177/0009922810394832

	Disorders Studies (Adult) 7.0.2		
Sites	Multi-site: 14 sites across the US (a mix of institutional sites and private practice centers)	Multi-site: 20 sites across the US (a mix of institutional sites and private practice centers)	SIMILAR
Enrollment	223 enrolled	348 enrolled	SIMILAR - the larger N in STARS study takes into account two arms. In Adults, sample size was determined by power calculations.
Stably on or off ADHD medications	Stably on or off stimulant medication (≥4 weeks) allowed Stably on or off non-stimulant medication (≥4 weeks) allowed	Stimulant medication use not allowed Use of non- stimulant ADHD medication not allowed	DIFFERENT – Another published study[11] demonstrated ADHD improvement occurred similarly in patients both stably on and off ADHD medications. This criterion was adopted into the adult study design to better simulate real-world user base The adult study allowed non-stimulant medication use as long as stability 4-weeks before and after study enrollment is maintained to better represent the diversity of patients who may use the device and to generalize to real-world user base.
Stably on or off nonpharmacological treatments	Stably on or off nonpharmacological treatments (≥4 weeks) allowed	Stably on or off nonpharmacological treatments (≥4 weeks) allowed	SIMILAR
Absence/Presence of comorbid psychiatric diagnosis and/or treatments that may confound	Presence of comorbid psychiatric diagnosis and/or treatments that may confound study not allowed	Presence of comorbid psychiatric diagnosis and/or treatments that may confound study not allowed	SIMILAR

[11] Kollins, S.H., Childress, A, Heusser, AC and Lutz, J. (2021). Effectiveness of a digital therapeutic as adjunct to treatment with medication in pediatric ADHD. npj Digit. Med. 4, 58. https://doi.org/10.1038/s41746-021-00429-0

study			
Absence/Presence of conditions that would prevent the proper use of the investigational product	Presence of conditions that would prevent the proper use of the investigational product not allowed	Presence of conditions that would prevent the proper use of the investigational product not allowed	SIMILAR
Primary Outcome Measure	Change in TOVA attention comparison score (ACS) from pre- to post-intervention	Change in TOVA attention performance index (API, also known as TOVA-ACS) from pre- to post-intervention	SIMILAR
Secondary Outcome Measures	Mean changes in: • ADHD-Rating Scale-IV (ADHD-RS) Inattention Subscale Score • ADHD-RS Total Scale Score	Mean changes in: • ADHD-RS Total Score • ADHD-RS Inattention Subscale Score • ADHD-RS Hyperactivity Subscale • BRIEF Working Memory percentile • BRIEF Inhibit percentile • Impairment Rating Scale (IRS) • Clinical Global Impression (CGI)	DIFFERENT –The predicate device used the Impairment Rating Scale (IRS) and the Clinical Global Impressions Scale (CGI) to assess functional impairment, but since the IRS is a parent reported measure and the CGI was not sensitive to treatment effects in the predicate study, neither was used in the subject study, which used the Adult ADHD Quality of Life (AAQoL) Scale as a measure of ADHD impairment in adults. Both studies had ADHD-RS as secondary measures. Whereas the STARS study listed multiple secondary measures, the adult study focused on ADHD-RS as the secondary measure, which the predicate study showed to be sensitive to the AKL-T01 treatment.

Table 2. Clinical Study Outcome Comparison Table

Outcome Measure	Clinical Study for EndeavorOTC (K233496)	Clinical Study used to support EndeavorRx (DEN200026)	Differences
	Adults (ages 18+)	STARS (ages 8-12)	
1. pre-post change score on TOVA ACS **(Positive change indicates improvement)**	6.46	0.93	Adults show nearly 6 times the improvement in TOVA-ACS than in STARS. Although the magnitude of benefit is different between EndeavorOTC and the predicate device, both devices show improvement in TOVA-ACS Score.
2. pre-post change score on ADHD-RS Inattention subscale **(Negative change indicates improvement)**	-5.1	-3.6	Greater mean change than STARS. Although the magnitude of benefit is different between EndeavorOTC and the predicate device, both devices show improvement in ADHD-RS Inattentive Scale Score, which did not reach a clinically meaningful threshold. Clinically meaningful improvement based on literature for the ADHD-RS is estimated at 10-point difference.[12]
3. pre-post change score on ADHD-RS Total Score **(Negative change indicates improvement)**	-8.3	-6.2	SIMILAR - Greater or comparable mean change to STARS.

[12] Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. Int J Methods Psychiatr Res. 2005;14(4):186-201. doi:10.1002/mpr.7

Table 3. Modified Intent-to-Treat (mITT and Intent-to-Treat (ITT) Analysis with Multiple Imputation (MI) of the Primary Efficacy Endpoint – TOVA-ACS Change from Baseline to Exit

Analysis	Baseline TOVA-ACS	Exit TOVA-ACS	Change from Baseline
STARS ITT Population			
n	179	170	169
Mean (SD)	-5.11 (0.22)	-4.16 (0.28)	0.93 (0.24)
95% CI			0.45, 1.40
p-value[1]			0.0002
Adult Efficacy Population (mITT)			
n	153	153	153
Mean (SE)	-8.739 (0.6089)	-2.279 (0.3978)	6.460 (0.5621)
95% CI			5.349, 7.570
p-value[1]			<0.0001
Adult Safety Population (ITT with MI[2])			
n	221	221	221
Mean (SE)	-8.644 (0.5249)	-2.489 (0.4542)	6.155 (0.5698)
95% CI			5.037, 7.273
p-value[1]			<0.0001

Abbreviations: CI = confidence interval; FCS = fully conditional specification ITT = intent-to-treat, also known as Safety Population, is all subjects enrolled in the study; mITT = modified intent-to-treat, also known as Efficacy Population, is all enrolled subjects with drop outs excluded; MI = multiple imputation; SE = standard error

[1] From a one-sample t-test of change greater than zero. Positive changes indicate improvement.

[2] Multiple imputation for participants with missing data at Day 42 was performed using FCS with 100 imputations and included covariates age, sex, race, ethnicity, education plan, age of ADHD symptom onset, concomitant stimulant use, treatment exposure defined as number of non-practice missions completed, and baseline TOVA-ACS value. Estimates of mean and standard error at baseline, exit and change from baseline were calculated for each imputation and combined using PROC MIANALYZE in SAS version 9.4.

Table 4. Clinical Safety Outcome Comparison Table - Safety Outcomes for Participants who received AKL-T01 in STARS-Adults (Safety Population[1]) and STARS-ADHD (DEN200026) studies

ADEs by Preferred Term n (%)	All Studies N = 401	Adults (K233496) N = 221	STARS-ADHD (DEN200026) N = 180	Comparison describing differences and a rationale why it is acceptable
Any ADE	23 (5.74%)	11 (5.0%)	12 (6.7%)	Compared to STARS study, fewer participants in the Adult study experienced treatment-emergent adverse device effects (TE-ADE) overall. The only ADE where adults reported higher incidence at greater than 1% was nausea. All other incidences (fatigue, somnolence, and arthritis) remain low at <1%. Therefore, both EndeavorOTC and the predicate device are both safe for their intended use.
Frustration tolerance decreased	7 (1.75%)	2 (0.9%)	5 (2.8%)	
Headache	6 (1.5%)	3 (1.4%)	3 (1.7%)	
Nausea	5 (1.25%)	4 (1.8%)	1 (0.6%)	
Dizziness	2 (0.5%)	1 (0.5%)	1 (0.6%)	
Emotional disorder	2 (0.5%)	0 (0%)	2 (1.1%)	
Aggression	1 (0.25%)	0 (0%)	1 (0.6%)	
Fatigue	1 (0.25%)	1 (0.5%)	0 (0%)	
Somnolence	1 (0.25%)	1 (0.5%)	0 (0%)	
Arthritis	1 (0.25%)	1 (0.5%)	0 (0%)	

[1] Safety Population, also known as ITT or intent to treat population, is all subjects enrolled in the study.

Substantial Equivalence Discussion:	EndeavorOTC has the same intended use and similar indications, technological characteristics, and principles of operation as the predicate device, EndeavorRx (DEN200026). Moreover, EndeavorOTC complies with the same special controls as the predicate Endeavor Rx (DEN200026) set forth in 21 CFR § 882.5803. The expanded age range and minor software changes do not raise different questions of safety or efficacy. Substantial equivalence was supported by clinical and non-clinical performance (verification and validation) tests, which complied with the requirements specified in the international and FDA-recognized consensus standards, ISO 14971, IEC 62304, and IEC 82304. The non-clinical testing included software testing, which verified the minor software changes in EndeavorOTC. Clinical testing validated the safety and effectiveness of EndeavorOTC for its intended use in the indicated patient age range of 18 years and older. The clinical trial results showed a significant improvement in the primary effectiveness measure, TOVA, a digitally assessed measure of sustained and selective attention. Results also showed improvements in ADHD symptoms as assessed in key secondary measures, the ADHD-RS inattention scale and ADHD-RS total score, which did not reach clinically meaningful significance estimated at 10-points in literature[13]. These results were similar to the findings of the prior clinical trial that supported the original clearance of EndeavorRx for 8-12 year-old patients under DEN200026. The clinical testing also showed no new or increased safety risks in the expanded patient population compared to the predicate device. The results of these tests demonstrate that EndeavorOTC is as safe and effective as its predicate device. Therefore, EndeavorOTC is substantially equivalent.
Benefit-Risk Profile:	No serious adverse events were reported. Of the 221 subjects who received AKL-T01 in the adult study supporting EndeavorOTC authorization for ages 18 years and above, 11 (5.0%) subjects experienced 13 treatment-emergent adverse device events (TE-ADE). Reports include 4 (1.8%) nausea, 3 (1.4%) headaches, 2 (0.9%) decreased frustration tolerance, and 1 each (0.5%) of arthritis, dizziness, fatigue, and somnolence. Three TE-ADEs (somnolence, fatigue, and arthritis) were considered unanticipated, and 3 TE-ADEs (1 occurrence of headache and 2 occurrences of nausea) resulted in study treatment discontinuation. All TE-ADEs were either mild or moderate in severity, and all were considered related to the study treatment.

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There were no serious adverse device events. All adverse events were resolved by the end of treatment.

EndeavorOTC showed a general improvement in attention associated with ADHD. The totality of the evidence demonstrated clinical benefit in attention, as measured by the TOVA in the adult population (18+ years) with ADHD with a demonstrated attention issue. Improvements in ADHD inattentive symptoms were comparable or greater than the improvements in ADHD inattentive symptoms seen in the pediatric population from the predicate studies. As noted, the risks associated with EndeavorOTC are minimal.

For EndeavorOTC, the AE rates were low, in mild-moderate severity range. There were no SAEs, and all TE-ADEs were resolved by the end of the clinical trial. Given the favorable safety profile, even small benefits in inattentive ADHD symptoms would justify use of the product.

The benefits of the EndeavorOTC have been found to outweigh the individual risks. After evaluating all benefits, risks and applicable considerations, it has been determined that the overall residual risk of the EndeavorOTC is acceptable, and the product is considered safe for use by the intended user within the intended use environment.